CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

1

Introduction: epidemiology, pathology and clinical presentation

Vincent Vander Poorten

In general in the head and neck, two major groups of malignant neoplasms can be recognized. A smaller but important group of neoplasms can be described as "glandular neoplasms," the majority arising in the thyroid, a minority in the salivary glands. These tumors are not considered in this chapter. This chapter deals specifically with the largest group of malignancies, so-called squamous cell carcinoma (SCC) of the head and neck (HNSCC). These account for about 90% of all head and neck cancers [1] and originate in the mucosal membranes of the upper aerodigestive tract. Squamous cell carcinoma also arises from the skin. Skin cancer is generally considered a separate entity, as is skin cancer of the head and neck.

Head and neck neoplasia observed less frequently include localized lymphoma, soft tissue and bone sarcomas, and neuroectodermal tissue tumors (paraganglioma, olfactory neuroblastoma, neuroendocrine carcinoma, malignant melanoma). As this volume deals specifically with HNSCC, the reader is referred to specific oncological literature for information on other neoplasms.

This chapter deals with the epidemiology, pathology and clinical presentation of premalignant and malignant head and neck neoplasms.

Epidemiology: frequency measures and risk factors

Incidence

Head and neck cancer, excluding skin cancer and Hodgkin and non-Hodgkin lymphoma, is the sixth most frequent cancer in the world. Approximately 500 000 new malignancies of the mucous membranes are registered per year (oral and pharyngeal cancer: 363 000 new cases and 200 000 deaths yearly; laryngeal cancer: 136 000 new cases and 73 500 deaths yearly) [2]. This represents 6% of the global incidence of

Squamous Cell Cancer of the Neck, ed. Robert Hermans. Published by Cambridge University Press.
© R. Hermans 2009.

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

Table 1.1. Proportion of malignant tumors (% of total) arising in the major anatomic sites in the Flemish population of Belgium

Type	Male (%)	Female (%)
Oral SCC	33	34
Oropharyngeal SCC	11	7
Hypopharyngeal SCC	7	3
Laryngeal SCC	34	10
Nasopharyngeal–paranasal sinuses	6	5
Salivary gland	4	7
Thyroid	5	34

SCC, squamous cell carcinoma.

cancer. In the European Union in 1997, 5% of the global cancer burden encountered was caused by oral, pharyngeal and laryngeal cancer [3]. The larynx and oral cavity are most frequently involved, as indicated by the population-based numbers of the Flemish Cancer Registry in Belgium (Table 1.1) [4]. Overall, the incidence is dependent on gender and geography. In HNSCC, there is a definite male preponderance. For example, a male/female ratio of 10/1 is observed in the incidence of laryngeal SCC [5]. There is an important geographical variation in the incidence of specific head and neck subsites for cancer. For example, hypopharyngeal SCC is typically more frequent in northern France (10/100 000 males per year) than in the USA (2/100 000 males per year). The yearly incidence of laryngeal cancer in northern Spain (20/100 000) is approximately 200 times the incidence in certain regions in China (0.1/100 000) [6]. Apart from differences in genetic susceptibility, a different prevalence of strong risk factors (e.g., tobacco use, Calvados drinking) largely explains these geographical differences. Also a large part of the observed differences in incidence among races (lower incidence in Caucasian versus African Americans [7]), and observed gender differences, can be attributed to marked differences in exposure to risk factors [8].

Risk factors

Chronic use of tobacco and alcohol is the main cause of the development of HNSCC. Epidemiologically, the strong association with the induction of the disease and the very high prevalence of the factors among the population explain the strength and the impact of the causal relationship that is observed. Tobacco and

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

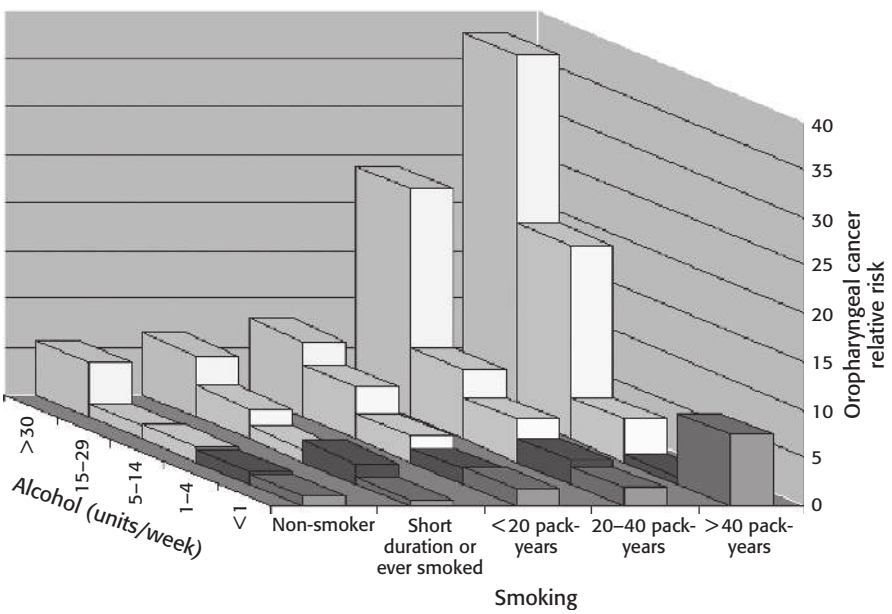

Fig. 1.1. Relative risk for development of oral and pharyngeal cancer for males according to amount of tobacco and alcohol used. (Based on data from W.J. Blot *et al. Cancer Res* 48 (1988), 3282–3287, with permission.)

alcohol are independent risk factors that act in a multiplicative way when used together. Figure 1.1 illustrates the 5.8 times increased risk for development of oral and pharyngeal cancer in non-smokers who consume 30 or more drinks per week and the 7.4 times increase in risk observed in non-drinking smokers with a history of smoking 20 cigarettes per day for 40 years. A person combining these two bad habits multiplies these relative risks to a 38 times increased risk [9]. After stopping the use of tobacco, the risk for oral mucosal dysplasia and cancer takes 15 years to reach the level of the population that never smoked [10].

Tobacco contains the carcinogens aldehydes, polycyclic aromatic hydrocarbons and nitrosamines. Nitrosamines are alkylating agents that induce mutational events. Alcohol acts as a solvent, enhancing permeation of toxic substances in tobacco into the cells of the mucosa. Alcohol is directly carcinogenic following mucosal enzymatic reduction (by alcohol dehydrogenase) to acetaldehyde. The oro- and hypopharyngeal mucosal surfaces especially are at risk for alcohol-induced carcinogenesis [11]. The mucosa of the glottic larynx does not have direct contact with the carcinogen and, therefore, only very high alcohol consumption is found to increase HNSCC risk independently. Alcohol intake creates exposure to other carcinogenic compounds such as tannin in wine and nitrosodimethylamine in

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

beer. Furthermore, high intake of these beverages implies nutritional deficiencies, which also increase the risk of HNSCC development by losing the proven protective effect of high intake of fruits and vegetables. A diet rich in fresh fruit and vegetables has been estimated to reduce the incidence of HNSCC by 50–70% [12]. Especially protective are dark yellow vegetables, citrus fruits and carotene-rich vegetables (fresh tomatoes, pumpkins, carrots). These vegetables contain crucial antioxidant micronutrients such as vitamin C, vitamin E, beta-carotene, and flavonoids [13]. High-fibre intake [12] and olive oil [14] are also suggested to have protective effects.

All the factors enumerated so far are associated with socio-economic status, which, therefore, itself is also strongly associated with the development of HNSCC. Three out four patients with HNSCC are located in the lower social classes, in terms of level of education and income. One in three patients has no partner and one in six patients is unemployed at the time of diagnosis. This social situation is strongly linked to the combination of the direct risk factors tobacco, alcohol, poor dietary habits and lower level of oral hygiene. Once HNSCC has developed, people in lower socio-economic groups will find their way to the health system with more difficulty because of less education, and will present with more advanced stages of disease. Stage at presentation is the strongest negative prognostic factor for outcome of treatment in HNSCC. Treatment of advanced disease often has a serious physical and psychological impact. A serious effort is needed to adapt to the resulting altered body image, to integrate back into society and to realise the change in lifestyle needed to reduce the risk of a second primary HNSCC. Unfortunately, following treatment, patients in lower social classes have less support to face this challenge. Rehabilitation is often very difficult for many of these patients [15]. A lower socio-economic environment is a strong negative prognostic factor for the results of treatment and also for survival in general because of the lasting effect of the comorbidities that result from the former lifestyle (e.g., liver disease, pulmonary insufficiency, atherosclerosis).

Viral infections also have been implicated in the pathogenesis of HNSCC [14]. Human papilloma virus (HPV) DNA is prevalent in approximately 50% of patients with oral cancer and in 72% of those with oropharyngeal cancer. Relative risks up to 6.2 for development of oral cancer have been reported, and recently a relative risk of 12 for the development of oropharyngeal cancer has been confirmed. Type 16 HPV seems particularly associated with the development of oropharyngeal SCC, both in patients with and patients without the risk factors tobacco and alcohol [16]. It does not seem unrealistic to expect an effect of HPV vaccination on the future incidence of these tumors. Epstein–Barr virus (EBV) has been strongly associated with nasopharyngeal

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

cancer. Antibody titers for EBV are much higher in cases than in controls, and biopsy specimens of undifferentiated nasopharyngeal carcinoma are 100% EBV positive and monoclonal for this virus [17]. Following treatment,EBV antibody titers are used to follow patients for disease recurrence. Patients infected with the human immunodeficiency virus (HIV) have an increased risk of developing HNSCC and Kaposi sarcoma.

Occupational factors have been implicated in HNSCC development. Working in industry with higher exposure to aromatic amines and phenoxy herbicides creates an elevated risk for all sites. The rate of development of SCC of the sinonasal tract is increased 250 times in workers exposed to nickel [18]. Among environmental factors, chronic sun exposure causes development of skin and lip cancer.

Pathology

The first step is to identify the tumor as SCC. The pathologist then has to identify prognostic factors such as the grade of differentiation, perineural or vascular invasion, and the assessment of the resection margins following surgery.

Epithelial neoplasms of the mucous membranes

Premalignant lesions

Premalignant lesions will usually not be visualized on routine imaging studies. Different forms of leukoplakia are distinguished: homogeneous leukoplakia and non-homogeneous leukoplakia (Figs. 1.2 and 1.3, respectively).

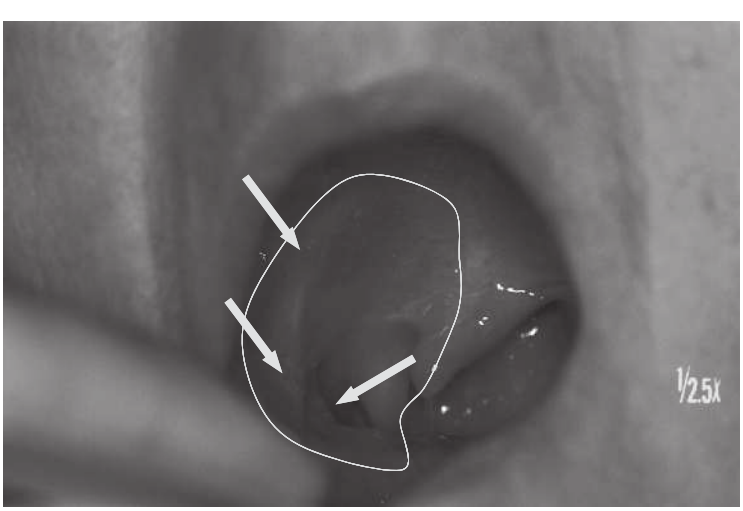

Fig. 1.2. Erythroplakia (encircled) with areas of nodular leukoplakia (arrows) of the tonsil, glossotonsillar sulcus, anterior tonsillar pillar and hard and soft palates. Color version in plate section.

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

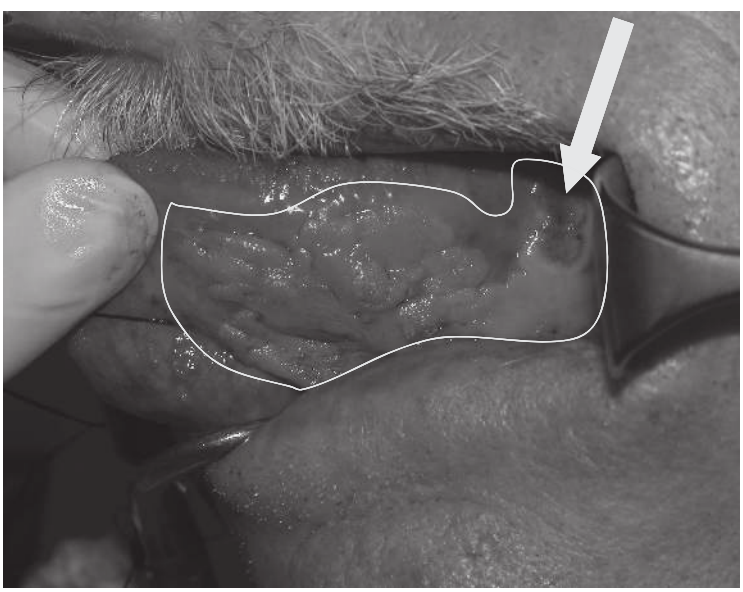

Fig. 1.3. Non-homogeneous leukoplakia (encircled) with area of invasive carcinoma (arrow) of the lateral tongue. Color version in plate section.

Leukoplakia is "a white plaque or patch that cannot be characterized, clinically or histopathologically, as any other disease" [19]. It should be impossible to scrape off the lesion, unlike candidal patches. Another condition for this diagnosis is that the lesion should not be associated with any physical (frictional keratosis, candidal leukoplakia) or chemical agent, except tobacco.

Homogeneous leukoplakia is the most frequent observation, corresponding microscopically to hyperortho- or hyperparakeratosis, and rarely shows associated dysplasia. The yearly rate of malignant transformation of homogeneous leukoplakia is estimated to be between 2% and 6% in the Western world and is higher in older, female patients and when the lesion persists for a longer time.

Non-homogeneous leukoplakia (nodular leukoplakia, erythroplakia, proliferative verrucous leukoplakia) is less frequently observed but is usually associated with dysplasia and is, therefore, much more prone to becoming invasive [20]. The rate of malignant transformation in non-homogeneous (speckled) leukoplakia (Fig. 1.3) and erythroplakia can exceed 50% [21].

Microscopically, epithelial hyperplasia, dysplasia and carcinoma in situ are sought. Dysplasia is described as "mild" where there is an increased number of mitotic figures and an abnormal cytological appearance only in the basal layer of the epithelium, whereas suprabasal mitosis and cytological abnormality indicates "moderate" dysplasia. In "severe" dysplasia, the atypical cells with mitotic activity

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

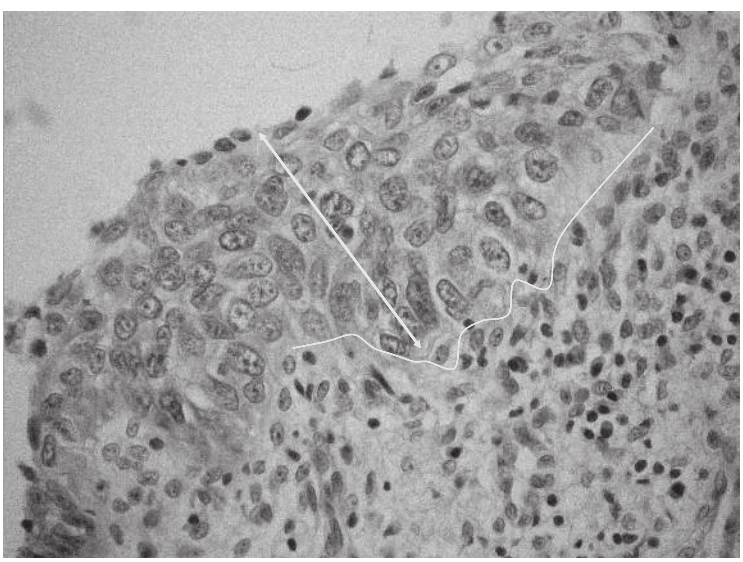

Fig. 1.4. Carcinoma in situ. Loss of an orderly nuclear mosaic pattern, increased nuclear/cytoplasmic ratio and an irregular random nuclear placement can be observed in all suprabasal cells (double arrow). Yellow line shows lamina basalis of epithelium. Color version in plate section. (Courtesy of Raf Sciot.)

and abnormal cytological features such as loss of an orderly nuclear mosaic pattern, decreased nuclear/cytoplasmic ratio and an irregular random nuclear placement, can be observed from the basal to the most superficial layers. The term carcinoma in situ indicates that all suprabasal cells are abnormal but signs of invasion can still not be detected (Fig. 1.4).

Malignant lesions

Entities seen less frequently but with a specific clinical behavior are verrucous carcinoma, papillary SCC, basaloid SCC and sarcomatous SCC, increasingly aggressive in that order. Verrucous carcinoma is an exophytic papillomatous SCC that is low grade, very well differentiated and without known potential for regional or distant metastasis [22]. Papillary SCC displays an exophytic growth with a poorly differentiated cell layer lining a central fibrovascular core. The behavior of this type of tumor is more aggressive than verrucous carcinoma in that metastases occur. Basaloid SCC and sarcomatoid SCC are highly aggressive variants of SCC.

Most of the malignancies of the mucous membranes are simply called "invasive squamous cell carcinoma" and can be graded as well, moderately and poorly differentiated, paralleling the amount of keratin formation by cells (Fig. 1.5). Cells in SCC, by definition, produce intercellular bridges. Absence of these intercellular bridges is one of the features of undifferentiated carcinoma of the upper aerodigestive tract. This type of tumor occurs most frequently in the nasopharynx.

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

Table 1.2. Histopathological negative prognostic factors in HNSCC head and neck squamous cell carcinoma

Increasing (p)TNM classification: size of primary tumor, number/laterality of positive nodes, size of largest node
Vascular invasion
Perineural growth
Involved resection margins, e.g., less than 5 mm is considered "close margins" in oral cancer
Increasing tumor thickness
Invasive front, i.e., infiltration of the submucosa (Fig. 1.5)
Loss of differentiation
Endophytic worse than exophytic growth pattern
Field cancerization
Increasing mitotic index
Presence of extracapsular spread in metastatic lymph nodes

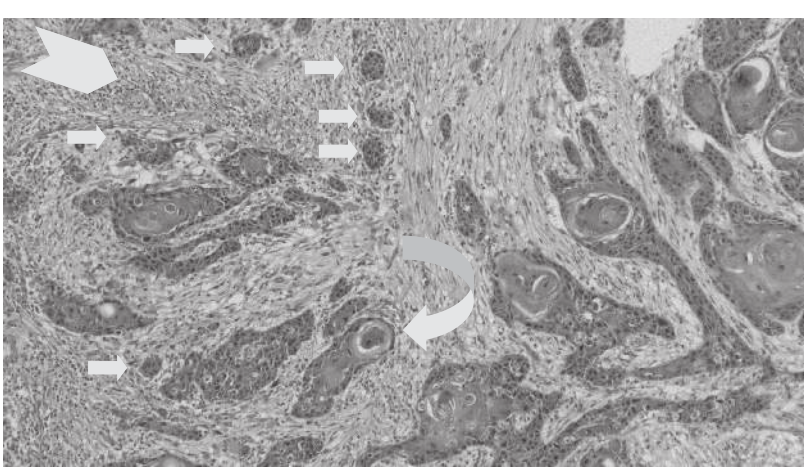

Fig. 1.5. Invasive squamous cell carcinoma. Tumor islets infiltrate the submucosal tissue (small arrows); there is an intense mononuclear inflammatory reaction (large arrowhead) and the formation of keratin pearls (curved arrow). Color version in plate section. (Courtesy of Raf Sciot.)

The most important microscopic findings to be determined following resection of a primary HNSCC and the regional lymph nodes are listed in Table 1.2. These findings are negatively associated with prognosis, so their routine determination during microscopical analysis contributes to the decision making concerning the need for further therapy, the particular postoperative radiotherapy and whether this is with or without chemotherapy.

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

Clinical presentation

The clinical presentation of a patient with this specific group of malignancies typically depends on the anatomical site of origin of the tumor. Usually, there will be involvement of the local sensory innervation or function of the aerodigestive tract, resulting in typical symptoms.

Each site of origin also has a regional lymphatic drainage system and, therefore, depending on the site of origin, regional metastatic disease in the neck is common at the time of presentation [23]. Conversely, in patients where the only symptom is a mass in the neck, the site of regional metastasis can point to the primary site. The typical association between a specific site of origin and the corresponding preferred level of regional lymph node metastasis is shown in Fig. 1.6. The locoregional extent is typically summarized in the UICC TNM classification, the last edition dating from 2002 [24]. The classification rules for attributing a HNSCC lesion to a specific T category differ according to the anatomic subsite in which the neoplasm arises, and this will be discussed in the dedicated subsequent chapters. The N classification is universal for all sites except for nasopharyngeal carcinoma, as will also be discussed later.

Clinical presentation at diagnosis

Patients with *glottic* laryngeal cancer tend to present at an earlier stage, given the effect of even a small vocal cord lesion on voice quality. This early presentation in combination with a relatively sparse lymphatic drainage corresponds to a low incidence of regional metastasis at presentation. This accounts for the observed good prognosis of HNSCC at this site. Five-year survival rates following radiotherapy or surgery range from 70 to 100% (Fig. 1.7) [25].

As pointed out under "risk factors", many patients with *supraglottic laryngeal, oral* and *pharyngeal* cancer will present at an advanced stage of their disease because of the late occurrence of symptoms. A comparison of this marked difference in stage at presentation of patients with glottic versus supraglottic cancer in the Memorial Sloan-Kettering Cancer Center [26] is shown in Fig. 1.8. Supraglottic laryngeal cancer will produce hoarseness only late in its development, by mucosal extension to the vocal cord, the arytenoid or the cricoarytenoid joint, or by submucosal extension to the paraglottic space. Other typical symptoms of advanced glottic and supraglottic laryngeal cancer, but also of oro- and hypopharyngeal cancer, are respiratory obstruction, hemoptysis and referred otalgia. Dysphagia and odynophagia

© in this web service Cambridge University Press & Assessment www.cambridge.org

CAMBRIDGE
Cambridge University Press & Assessment
978-0-521-88691-8 — Squamous Cell Cancer of the Neck
Edited by Robert Hermans
Excerpt
More Information

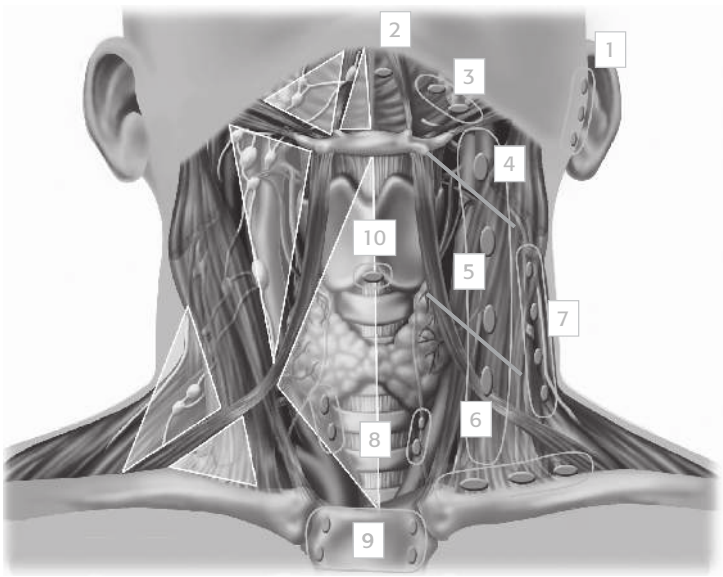

Fig. 1.6. Typical association between a specific site of origin and the corresponding likely level of regional lymph node metastasis in cancer of the head and neck. 1. Parotid nodes: primary tumors in forehead and anterior scalp skin, in the parotid gland. 2. Level Ia, medially from anterior belly digastric: primary in lower lip, lower alveolar crest, anterior floor of mouth. 3. Level Ib between anterior and posterior belly digastric: primary in skin of face and nose, oral cavity, paranasal sinuses, submandibular gland. 4. Level II, inferior of posterior belly digastric, above hyoid bone, medial of sternocleidomastoid muscle (above upper green line): primary in nasopharynx, oral cavity, oropharynx, supraglottic larynx, hypopharynx. 5. Level III, below hyoid, above caudal border cricoid, medial of sternocleidomastoid muscle: primary in nasopharynx, larynx, hypopharynx, cervical esophagus, thyroid gland (below upper green line and above lower green line). 6. Level IV, below cricoid, above clavicle, medial of sternocleidomastoid muscle: primary in nasopharynx, thyroid, esophagus, lung, breast. 7. Level V, laterally from sternocleidomastoid muscle: primary in nasopharynx, thyroid, esophagus, stomach, lung, breast. 8. Level VI, central compartment above thoracic inlet, lymph nodes: primary in larynx, hypopharynx, cervical esophagus or thyroid. 9. Level VII, upper mediastinal nodes above innominate artery: primary in thyroid or subglottic larynx, hypopharynx, cervical esophagus. 10. Prelaryngeal, delphian node: primary in larynx or in thyroid. Color version in plate section. (Courtesy of Pierre Delaere.)

are typically observed in supraglottic laryngeal, oro- and hypopharyngeal cancer, but all usually relatively late in the development of the disease. As already discussed, once symptoms occur, the often compromised social situation will make access to the medical system more difficult and further delay diagnosis and advance the stage at diagnosis.

Patients with *oral cavity* SCC will usually present with an exophytic (Fig. 1.9) or endophytic (Fig. 1.10) ulcerative lesion; endophytic tumors are associated with

© in this web service Cambridge University Press & Assessment www.cambridge.org